EPA RESPONSE
TO EXTERNAL PEER REVIEW COMMENTS

on the

DRAFT AQUATIC LIFE AMBIENT WATER QUALITY CRITERIA FOR CADMIUM – 2015

November 19, 2015

Office of Water
U.S. Environmental Protection Agency
Washington, DC

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1 INTRODUCTION

EPA submitted its *Draft Aquatic Life Ambient Water Quality Criteria (AWQC) for Cadmium – 2015* for contractor-led independent, external peer review from August 25 to September 14, 2015. The external peer reviewers provided their independent responses to EPA's charge questions. This report documents the EPA's response to the comments provided to EPA.

This report presents the four peer review charge questions and individual reviewer comments (verbatim) in Sections 2.1 through 2.4. Section 2.5 presents additional minor comments provided by one reviewer. New information (e.g., references) provided by reviewers is presented in Section 3. EPA separated each reviewer's comments by charge question into distinct topics and responded to each topic individually, and also indicated how the draft cadmium criteria document was revised in response to peer reviewer comments.

1.1 BACKGROUND

EPA's Office of Water is charged with protecting ecological integrity and human health from adverse anthropogenic, water-mediated effects, under the purview of the Clean Water Act (CWA) Section 304(a)(l). The Agency has been working to update water quality criteria to protect aquatic life and aquatic-dependent wildlife from the presence of cadmium in freshwater and estuarine/marine environments in order to reflect the latest scientific knowledge.

EPA's AWQC for cadmium presents draft acute and chronic criteria expressed as concentrations of cadmium in fresh and estuarine/marine waters (dissolved). The 2015 draft cadmium criteria document is an update to the 2001 cadmium criteria. The 2015 draft incorporates additional toxicological data for cadmium, while using the same criteria derivation process that was used in 2001.

1.2 PEER REVIEWERS

An EPA contractor identified and selected five reviewers who met the technical selection criteria provided by EPA and who had no conflict of interest in performing this review.

The EPA contractor provided reviewers with instructions, the review document (including appendices), the charge to reviewers) prepared by EPA, and supporting reference materials as described in the charge. Reviewers worked individually to develop written comments in response to the charge questions.

1.3 REVIEW MATERIALS PROVIDED

- Internal Draft Cadmium AWQC_ 042115 (081315).pdf
- Internal Draft Cadmium AWQC_Appendicies_7 1 15 (081315).pdf
- Appendix K Issue Summary Regarding Test Conditions and Methods...H. Azteca.pdf
- Internal Draft Cadmium AWQC_References_11 4 14 (081315).pdf

Background/Supplemental Material (not for review, reference only)

- Cadmium Risks to Freshwater (Mebane 2010).pdf

1.4 CHARGE QUESTIONS

1. Please comment on the overall clarity of the document and construction as it relates to the derivation of each criterion.

2. Please comment on the technical approach used to derive the draft cadmium criteria; is it logical, does the science support the conclusion, and is it consistent with the protection of freshwater and

estuarine/marine aquatic life from acute, chronic, and bioaccumulative effects? Are the methods described in the document scientifically sound?

3. Please comment on the data used to derive the revised criteria, including data adequacy/comprehensiveness, and the appropriateness of the data selected and/or excluded from the derivation of the draft criteria. Is the data used correctly for the intended purpose? Are there other relevant data that you are aware of that should be included? If so, please provide the data along with supporting information.

4. Are the derived criteria appropriately protective of listed species and commercially and recreationally important species, particularly as the criteria relates to salmonids?

2 External Peer Reviewer Comments and EPA Responses, Organized by Charge Question

The following tables list the charge questions submitted to the external peer reviewers, the external peer reviewers' comments regarding those questions (broken into distinct topics), and EPA's responses to the peer reviewers' comments. EPA revised the 2015 draft considering the external peer review comments, and noted in the table where the document was edited.

2.1 CHARGE QUESTION 1

1. Please comment on the overall clarity of the document and construction as it relates to the derivation of each criterion.

Reviewer	External Peer Reviewer Comments Regarding Charge Question 1	EPA Response	Revision Location in 2015 Draft Cadmium Criteria Document
Reviewer 1	This report makes for very dull reading, but it is well-written and it is usually clear what the author is trying to say. There are no insightful comments or new ideas presented in this report, but the report is laid out in a clear, logical fashion.	Thank you for your comment.	No edit needed.
Reviewer 2	Overall the document is relatively clear with formatting in a risk assessment format which allows the reader to evaluate each criteria. Of minor concern was the lack of inclusion of emerging materials as sources of cadmium such as quantum dots which do make up photovoltaic substances (mentioned). However, the increased use of these materials as "inorganic" Cd sources and the uncertainties surrounding the potential absorption and effects of these materials to aquatic organisms needs some discussion.	Information regarding quantum dots has been added to the document.	Section 2.1
Reviewer 2	In addition, some inconsistencies were noted with regard to sub-lethal effects mentioned in the Estuarine/Marine Acute section. While present in this section, discussions of sublethal effects were largely omitted in the Freshwater sections and chronic sections of both water types.	The Estuarine/Marine Acute section was revised to remove inconsistencies. Additionally, information about sublethal effects in other media was added to the appropriate sections of the document.	Section 5.1 Section 5.2 Section 5.4 Section 5.5

Reviewer 2	There was also inconsistencies with regard to the use of flow-through vs. static exposures and whether more or less uncertainty is involved in utilization of the values. For example, flow-through methods were stated for *Salmo trutta*, but methods for *Morone* were static or static-renewal. One would clearly suggest the flow through values should be given greater weight with regard to uncertainty assessments. As it reads right now, it appears there are no differences between using static or flow-through exposures.	Data selected to calculate the SMAV for each species follows 1985 Guidelines recommendations. Specifically, flow-through measured exposures are preferred and selected for use over static and static-renewal exposure studies. If only static or static renewal exposure studies are available, EPA considers the study data and determines whether the study is acceptable for inclusion considering factors, such as known compound stability and other relevant information presented by the study author. EPA's goal is to consider and include as much high quality, scientifically defensible data in its assessments as possible in order to characterize potential response in a broad array of aquatic organisms. For example, if a species of concern had only static renewal data for acute studies, and EPA knew the compound was stable in water during the test duration, the data would be considered for inclusion if it met with the other data quality screens EPA.	No edits needed.

Reviewer 2	The inability to determine salinity relationships to toxicity is also a concern but it is likely due to varied salinity regimes confounded with temperature and solute constituents in experimental designs (see comments below). It is noteworthy that a 1ppt value is considered "estuarine" for the *Morone* value, when there are "freshwater" systems that likely have higher conductance than this value. There should also be some statement or better clarity documenting the lack of a standard salinity value being utilized to compare toxicity values. It appears that the most sensitive toxicity value is being used regardless of the salinity.	The current statement in the Executive Summary about the salinity relationship addresses this comment: "Available data suggest the acute toxicity of cadmium may be influenced by salinity, with a trend of decreasing sensitivity to cadmium with increasing salinity. However, this trend could not be definitively characterized and a mathematical relationship could not be described to define the dependency (See Section 5.4.1)." Text has been added to elaborate on why a salinity normalization approach is not being used in criteria development. The estuarine/marine value is intended to be applicable to the broad range of salinities present in non-freshwater systems. EPA will accordingly continue to use 1 ppt as the lowest salinity level for a salt water test. This salinity is consistent with Mitsch and Gosselink (1986) who classify a waterbody with a salinity of 0.5-5.0 ppt is oligohaline. Mitsch, W.J. and J.G. Gosselink. 1986. *Wetlands.* Van Nostrand Reinhold, New York. 539 pp.	Section 2.3.1 Section 5.4.1
Reviewer 2	Overall, the uncertainty analysis section should be extended to include aspects of uncertainty with the data used for the derivation of the criteria. As it stands presently, the emphasis seems to be more on justification of data not utilized for the derivations.	Data selection is consistent with the procedures presented in the 1985 Guidelines. The Effects Characterization section was revised to include further discussion about uncertainty in the criteria calculations.	Section 5.1 Section 5.2 Section 5.4 Section 5.5
Reviewer 3	In general, the document language is reasonably clear. However, throughout the document, there are several instances where certain decisions are made that appear to be rather arbitrary without sufficient justification as to how or why these decisions were made (see details below).	Thank you for your comment. Please see responses to specific comments.	No edits needed.
Reviewer 3	Minor comments: p. 8 and elsewhere: use mass units rather than ppm, ppb etc.	These values are mineral deposit concentrations in units reported by the author(s), but were changed to mg/kg based on the comment. There are no other uses of ppm or ppb in the document.	Section 2.1

Reviewer 3	p. 9: quantify concentrations found in impaired water (“several micrograms per liter” is vague)	The text has been revised to give a definitive value.	Section 2.1
Reviewer 3	p. 10: is the suggestion that precipitated/particulate forms of Cd that ultimately end up in sediments are not bioavailable?	Text was added to clarify that particulate forms of cadmium are potentially available to benthic feeders and sediment dwellers.	Section 2.2
Reviewer 3	p. 19: do data exist for any other salts of Cd that has been excluded?	The 1985 Guidelines note specific salts to test for metals; only these salts were used. According to the Manual of Instruction for Preparing Aquatic Life Water Quality Criteria Document, Stephan 1985, Section III. Defining the Pollutant, "for metals such as cadmium, chromium (III), and zinc, only data from tests on chloride, nitrate, and sulfate salts (either anhydrous or hydrated) should be used", therefore, other data for other cadmium salts were not included in the evaluation. Thus, studies conducted with cadmium acetate and cadmium borate salts were not used, nor were tests with nanoparticles and quantum dots. Stephan, C.E. 1985. Manual of instructions for preparing aquatic life water quality criteria documents. Draft report dated 12-12-85. U.S. EPA. Environmental Research laboratory, Duluth, MN. 49 pp.	No edits needed.

Reviewer 3	P.63: Please be explicit about how the constants in the equations are derived for both the CMC and CCC.	The reviewed draft contained explicit information about how the constants in the equations for the CMC and CCC were derived: The CMC=$e^{(1.103 \times \ln(\text{hardness})-4.247)}$ Where, 1.103 is the acute pooled slope and; -4.247 is calculated as =ln(CMC at 100 hardness) - (Pooled Acute Slope x (ln(100))) =ln(2.3)-(1.103 x 4.605) Similarly, the CCC=$e^{(0.8161 \times \ln(\text{hardness})-3.663)}$ Where, 0.8161 is the chronic pooled slope and; -3.663 is calculated as =ln(CCC at 100 hardness) - (Pooled Chronic Slope x (ln(100))) =ln(1.1)-(0.8161 x 4.605)	No edits needed.
Reviewer 3	P. 67: Define the values listed under the two tables: (S2, L, A)	Footnotes were added to the document to define the terms S, L and A. These terms are refer to the following: S = slope; L = intercept; A = lnFAV. FAV = Final Acute Value.	Section 4.3.1 Section 4.3.2 Section 4.4.1.
Reviewer 3	Major comments: p. 12: "Mebane (2014) conclude that, although there were not adequate data to establish acceptable tissue effects concentrations for aquatic life, cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish. The evaluation of direct exposure effects is therefore considered to be more applicable to the development of criteria for aquatic life." This line of reasoning is questionable on many levels. Establishing critical tissue effects thresholds that work across species is problematic, especially in invertebrates, because species vary in their abilities to store/sequester Cd in physiologically inert forms. However, this does not mean that bioaccumulated metals are non-toxic as is implied by the language in this document. I think Mebane is being grossly	EPA concurs with the reviewer about the difficulty in characterizing dietary exposure and establishing critical tissue effects thresholds for bioaccumulated metals. Text has been added to discuss these points and incorporate the work of other researchers, such as Mebane (2006), who discuss cadmium bioaccumulation and dietary exposure in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and	Section 5.6.1

	misquoted here (aside from the fact that there is no 2014 reference). Here are some quotes from his 2010 document that directly refute the underlined text above: "Thus the consequences of elevated tissue residues or effects of dietary exposures may be important when estimating protective thresholds for cadmium and other pollutants (McCarty and Mackay, 1993; Meyer and others, 2005)." P. 32 "A diet of cadmium-contaminated green algae *Chlorella sp* caused reduced growth in the amphipod *Hyalella azteca* in a recent study (Ball and others, 2006)." P. 38 "Dietary cadmium exposures appear to be an important risk for at least some invertebrates. The data reviewed on dietary effects of cadmium to invertebrates indicated that adverse effects could occur at concentrations realistic in cadmium-polluted waters". P. 38 "Toxicity to mayflies from feeding on cadmium-contaminated algal mats at environmentally realistic concentrations was observed (Irving and others, 2003). P. 38 I understand that dealing with dietary exposures is incredibly inconvenient in the context of the 1985 Guidelines, but pretending that they are not important in 2015 is irresponsible because we know better. The Irving et al., 2003 study referenced above provides direct evidence that diet derived Cd can be problematic in this aquatic insect example.	toxicological effect, and an acceptable tissue effect concentration cannot be defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	
Reviewer 4	I found the overall clarity of the document to be quite good. I especially appreciated the document being generally organized in a risk assessment format. I think this is very useful, particularly the Problem Formulation section that outlines various sources, potential exposure pathways and receptors. I hope EPA will use this overall structure for future criteria documents as well. I also like all of the comparisons to previous Cd criteria documents. This makes key changes to the criteria very transparent.	Thank you for your comment.	No edits

Reviewer 4	My only significant criticism of the overall format is that there are a number of redundancies where information is presented multiple times, often the exact same wording (for example, Section 5.4.1 is redundant of earlier text in the document). I encourage EPA to consider consolidating and reducing these redundancies.	The document was reviewed and revised to minimize redundant text.	Various locations
Reviewer 4	An additional minor point is that it is unclear how the data tables in the appendices are organized. They don't seem to be listed alphabetically by either common or scientific name. It would be useful if they were.	Data tables are organized as recommended by the 1985 Guidelines (phylogenetically) and text was added to each table in the Appendices to clarify this.	Appendices
Reviewer 5	Generally sufficient. Problem formulation section seemed a bit of a forced fit, as if added to satisfy a new stylist protocol.	Thank you for your comment.	No edits needed.

2.2 CHARGE QUESTION 2

2. Please comment on the technical approach used to derive the draft cadmium criteria; is it logical, does the science support the conclusion, and is it consistent with the protection of freshwater and estuarine/marine aquatic life from acute, chronic, and bioaccumulative effects? Are the methods described in the document scientifically sound?

Reviewer	External Peer Reviewer Comments Regarding Charge Question 2	EPA Response	Revision Location in 2015 Draft Cadmium Criteria Document
Reviewer 1	This report is rather antiquated in its thinking. It basically assumes that Cd is accumulated only from the aqueous phase rather than from both the aqueous phase and ingested food. Over the past 10-15 years, it has been shown that many toxicants, including Cd and other metals, can be bioaccumulated from food as well as from the aqueous phase. Indeed, a number of laboratory, field, and modeling studies have shown that diet can be the dominant source of metals for marine invertebrates and fish. The relative importance of diet has been shown to vary with species, but it is rarely a minor source and sometimes (for some fish species, for example) the predominant source. Moreover, once accumulated from diet, Cd can reach sensitive organs within animals that are not reached by Cd taken up from the aqueous phase. Therefore, the toxic response of an animal to either ambient Cd or body burden Cd can vary considerably, depending on whether the source is ingested food or solute in ambient water. Thus, dissolved metal may be sorbed onto exoskeletons in crustacean zooplankton (often the most sensitive species, as the author points out) but this does not directly affect the animal because the metal (Cd in this case) bound to chitosan on the exoskeleton does not interact with metabolic processes, whereas metal assimilated from ingested food can enter into internal tissues where it may interfere with a variety of metabolic and reproductive processes. I saw no acknowledgement of the possible significance of dietary Cd on aquatic (freshwater or marine) animals in this report, and	EPA concurs with the reviewer about the multiple potential exposure routes and the complexity of characterizing these routes and establishing critical tissue effects thresholds for bioaccumulated metals. Text has been added to discuss these points and incorporate the work of other researchers, such as Mebane (2006), who discuss cadmium bioaccumulation and dietary exposure in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and toxicological effect, and an acceptable tissue effect concentration cannot be defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	Section 5.6.1

	yet numerous papers describing such effects appeared in the reference section. In looking over appendices, many of these reports were not used, often for what appear to be spurious reasons or misinterpretations of studies. In some cases, dietary metals could be 1-2 orders of magnitude more toxic than dissolved metals to freshwater cladocerans and marine copepods, for example. In the case of Cd, an EC_{50} value of 5 nM (~0.5 µg/L) was observed in copepods in a study by Hook & Fisher (cited in this report) if the animal had been fed food exposed to that Cd concentration, whereas the measured LC_{50} value based on a dissolved Cd source was 200 times greater. Also, measuring growth or mortality, as is often the case in simple toxicity tests, would have missed the effect—rather the reproductive capability of the copepods was affected by the dietary Cd, but no mortality was observed at environmentally realistic concentrations. Because dissolved Cd concentrations are typically at very low concentrations in natural waters (at least 10-fold lower in surface seawater, for example), the lower EC_{50} value derived from dietary rather than dissolved sources still indicates that Cd is unlikely to cause toxic effects in most natural waters.		
Reviewer 2	With a few notable exceptions, the technical approach for the freshwater acute and chronic derivations appear valid. Incorporation of hardness normalization is warranted given the likelihood that Cd and Ca compete for similar biological and abiotic sites. In addition, the increased number of species extending the SSDs is also an excellent step forward in confirming proposed criteria.	Thank you for your comment.	No edits needed.
Reviewer 2	Of concern is the approach utilized for the chronic estuarine/marine values. Utilization of ACRs with freshwater fish or other organism to derive estuarine/ marine values is not appropriate, especially when the criteria concentrations are increased. It is also unclear why freshwater salmonid values were not utilized for the ACRs, as many reside in estuarine/marine environments (see salmonid comments below).	The use of a freshwater ACR to derive estuarine/ marine values is described as an acceptable approach in the 1985 Guidelines, and was used in the draft criterion document reviewed by the external peer reviewers. Based on the peer reviewer comment, the estuarine/marine ACR approach was re-examined and revised for the 2015 draft proposal for public comment. The revised FACR incorporates data for seven genus-level ACRs and was derived	Section 2.7.3 Section 4.4.2 Section 5.5.1

		using data for marine species and a diversity of freshwater species, many of which have taxonomically-related marine species. ACRs used to derive the FACR incorporate data for five freshwater fish species, three freshwater invertebrate species, and two acutely sensitive estuarine/marine mysids.	
Reviewer 3	Bioaccumulative effects of Cd are largely ignored in this document.	Text has been added to discuss these points and incorporate the work of other researchers, such as Mebane (2006), who discuss cadmium bioaccumulation and dietary exposure in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and toxicological effect, and an acceptable tissue effect concentration cannot be defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	Section 5.6.1
Reviewer 3	My comments for this section are divided into 2 parts: 1. The technical approach according to the 1985 Guidelines, and 2. The technical approach in light of our current understanding of cadmium bioaccumulation, effects, and deficiencies in the traditional testing approaches. The technical approach according to the 1985 Guidelines A. What is the rationale for use of EC20 values for the chronic toxicity assessment? I understand that a MATC approach	The endpoint for chronic exposure is the EC_{20}, which represents a 20 percent effect/inhibition concentration. This is in contrast to a concentration that causes a low level of reduction in response, such as an EC_5 or EC_{10}, which is rarely statistically significantly different from the control treatment. U.S. EPA selected an EC_{20} to estimate a low level of effect that would be statistically different from control effects, but not severe enough to cause chronic effects at the population	No edits needed.

	(based on NOEC and LOECs) has its issues, and I'm generally in favor of more statistically robust approaches such as the use of an EC level based on entire datasets. But why is a 20% effect level chosen here? This value seems rather high. There should be some rationale for choosing this value, and this rationale should be clearly articulated in the text. How do we know that a 20% effect level has no impacts at the population level?	level (see U.S. EPA 1999c). Reported NOECs (No Observed Effect Concentrations) and LOECs (Lowest Observed Effect Concentrations) were only used for the derivation of chronic criterion when an EC_{20} could not be calculated for the genus. A NOEC is the highest test concentration at which none of the observed effects are statistically different from the control. A LOEC is the lowest test concentration at which the observed effects are statistically different from the control. When LOECs and NOECs are used, a Maximum Acceptable Toxicant Concentration (MATC) is calculated, which is the geometric mean of the NOEC and LOEC. Regression analysis was used to characterize a concentration-effect relationship and to estimate concentrations at which chronic effects are expected to occur. For the calculation of chronic criterion, point estimates were selected for use as the measure of effect over a MATC, as MATCs are highly dependent on the concentrations tested. Point estimates also provide additional information that is difficult to determine with an MATC, such as a measure of effect level across a range of tested concentrations. U.S. EPA. 1999c. 1999 Update of ambient water quality criteria for ammonia. EPA-822-R-99-014. National Technical Information Service, Springfield, VA.	
Reviewer 3	Only 3 species (all fish) were used to generate the hardness correction for the freshwater chronic toxicity data set. *D. magna* and *P. promelas* data were not used because only MATCs were available and not EC20s. Is it not possible to estimate EC20's from these datasets? The use of only 3 species to make this very important hardness adjustment would seem to add a significant level of uncertainty to the final analysis, especially since 2 of species used have divergent slopes. ANCOVA (p=0.08) based on data from 3 species was used to say that the slopes 0.32, 1.46 and 1.08 are not different and can be pooled. Is this defensible? Shouldn't a conservative slope estimate be chosen here…. especially in	EC_{20}s could not be estimated for these species (data not provided in paper). EC_{20} point estimates were preferentially selected for use over a NOEC or LOEC as the measure of effect, as NOECs and LOECs, which are the basis of the MATCs, are highly dependent on the test concentrations selected. Furthermore, point estimates provide additional information that is difficult to determine using NOEC and LOEC effect measures, such as a measure of effect level across the range of tested concentrations, and the confidence intervals around those measures of effect. Correspondence has been sent to the authors who did not	Section 3.1.2 Appendix C

	light of the fact that a 20% effect level is much higher than an MATC or EC05 would be?	provide raw data for their studies, so EC_{20}s can be calculated if the data are available. Additional EC_{20}s were calculated based on their responses. An additional analysis was conducted to determine if the inclusion of 3 MATCs from the Chapman Manuscript for *D. magna* could be included in the hardness relationship along with the new EC_{20}s. This additional data supported the same conclusion that a pooled slope could be generated with a slightly different slope of 0.7977. Values were edited to reflect this new pooled slope.	
Reviewer 3	The most acutely sensitive marine genus, Tigriopus was not used in the analysis. The rationale was that it falls below the 5th percentile of the distribution. Isn't the whole point of the SSD to determine what is protective of 95% of the species? (Not 95% of the remaining taxa after sensitive taxa are arbitrarily removed from the dataset). Shouldn't all of the data be used here?	The 1985 Guideline recommendations were followed in that the four GMAVs closest to the 5th percentile are used to estimate the FAV.	Section 2.5 Section 2.7.2
Reviewer 3	The use of 2 ACRs from freshwater species in the development of a marine chronic criterion is dubious on many fronts. The justification for doing this needs to be articulated. If justifiable, the authors should then justify their choices as to why these 2 species were chosen. The reason given in the text is that the freshwater species were chosen on the basis of being acutely sensitive. However the purpose of ACRs is to evaluate the potential for the chemical to cause chronic toxicity. Use of an acutely sensitive species for ACR choice should theoretically result in species with low ACRs, and in this case, this is borne out. The freshwater invertebrate *L. silquoidea* has a reported ACR of 2.727, suggesting that is chronically not very toxic. However, the ACRs for most species are considerably higher: (see below) Mebane (2010) list ACRs for freshwater invertebrates:	The use of a freshwater ACR to derive estuarine/ marine values is consistent with the1985 Guidelines. However, based on the peer reviewer comment, the estuarine/marine ACR approach was re-examined and revised in the 2015 draft proposal for public comment. The revised FACR incorporates data for seven genus-level ACRs and was derived using data for both marine species and a diversity of freshwater species, many of which have taxonomically-related marine species. The revised FACR of 8.291 was derived from a geometric mean of genus-level ACRs for the following: • Estuarine/marine mysids, *Americamysis bahia* and *A. bigelowi* • Cladocerans, *Ceriodaphnia dubia* and *Daphnia* (*D. magna* and *D. pulex*) • Mottled sculpin, *Cottus bairdii*	Section 2.7.3 Section 4.4.2 Section 5.5.1

	Ephemerella: 158.67 Physa: 47.6 Aplexa: 28.5 and 47.87 Ceriodaphnia: 12.41 and 31.5 Daphnia: 65, 155, 112, 13 Hyalella: 17.5 This document lists the following freshwater invertebrate ACRs: Aplexa: 49.7 Lymnea: 12.81 Ceriodaphnia: 19.82 Daphnia: 57.3 With all of these values to choose from, 2.727 is clearly not a representative ACR for freshwater invertebrates. Since the use of a "mean ACR" is being applied across taxa, shouldn't the values be representative? Would it make sense to have higher ACRs apply to invertebrates and lower ACRs apply to fish since fish generally have low ACRs and inverts generally have high ACRs?	Salmonids, *Oncorhynchus* (*O. mykiss*, *O. tshawytscha*) and *Salmo* (*S. trutta*) • Fathead minnow, *Pimephales promelas* The seven ACRs differ by a factor of ≤ 11.95, which approximates the factor of 10 or less recommended by the 1985 Guidelines. The ACRs for salmonids were less than 2.0 and were therefore raised to 2.0 to be consistent with the 1985 Guidelines. The ACRs for the other freshwater species were not used for the revised FACR because they have no taxonomically-related marine species (e.g., pulmonate snails) and/or the ACRs appear to be outliers. The description of and rational for the new estuarine/marine ACR approach is provided in the post-peer review 2015 draft document.	
Reviewer 3	Technical approach based on what we understand about the world post 1985: Cadmium has been demonstrated to be toxic to practically every in vitro system it has been tested in. We strive to limit human dietary exposures in part because it is a known carcinogen and is nephrotoxic after dietary exposure. Effects of Cd on antioxidant physiology are well described in several species including aquatic insects. <u>What evidence can we point to suggest that bioaccumulated Cd is not toxic to aquatic organisms? This is a fundamental flaw in this document.</u>	Text has been added to discuss these points and incorporate the work of other researchers, such as Mebane (2006), who discuss cadmium bioaccumulation and dietary exposure in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and toxicological effect, and an acceptable tissue effect concentration cannot be defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic	Section 5.6.1

		invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	
Reviewer 3	We have a major and important disconnection between what traditional laboratory tests (using only direct aqueous exposures) and what field ecologists tell us about metal effects in aquatic insects. Because insects are such important players in freshwater ecosystems, and are the focus of CWA-driven biomonitoring programs, we have numerous examples of stream community structure being impaired by metal exposures. Yet lab (aqueous) tests generally suggest that insects are insensitive to Cd. Work in our laboratory has used Cd uptake and depuration kinetics to clearly demonstrate that 96 hour exposures are insufficient to elicit toxicity in aquatic insects are ecologically relevant concentrations (Buchwalter et al. 2007, Buchwalter et al. 2008, Poteat and Buchwalter 2014, Poteat and Buchwalter 2014). We have also shown that periphyton is a major sink for Cd, and is readily bioaccumulated in insects (Xie et al. 2010). We have also showed that Cd exposure does not negatively affect Ca transport in insects (Poteat and Buchwalter 2014) (as it is known to do in acutely sensitive taxa), and Ca provides little protective effects on Cd uptake (Poteat et al. 2012). Finally, we show that diet derived (but not water derived) Cd affects antioxidant physiology suggesting that dietary exposures may be more challenging to aquatic insects that aqueous exposures (Xie and Buchwalter 2011). These findings mirror those of Irving et al., 2003. All of these findings point towards short-term, water-only exposures are insufficient for evaluating metal toxicity in this important faunal group (see (Poteat and Buchwalter 2014) for discussion of these findings).	Criteria were derived considering lab water-based exposures using procedures that are consistent with the 1985 Guidelines. Additional discussion has been added to address the uncertainty of using lab-based tests to determine protective field concentrations and the importance of dietary exposures to this faunal group. In addition, generally good agreement has been reported for microcosm studies/whole effluent toxicity test results with corresponding field observed effects (Clements and Kiffney 1996; Clements et al. 2002; Norberg-King 1986). Mebane (2006) compared chronic criterion values and apparent effects values from ecosystem studies and field surveys and concluded that the data showed mostly good agreement between the laboratory-based predictions and effects observed in the field surveys or ecosystem experiments. EPA concurs with the reviewer about the importance of considering the dietary exposure route. Text has been added to discuss this and incorporate the work of other researchers, such as Mebane (2006), who discuss cadmium bioaccumulation and dietary exposure in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and toxicological effect, and an acceptable tissue effect concentration cannot be	Section 2.5 Section 5.1.3 Section 5.6.1

		defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	
Reviewer 4	Overall yes, I think the technical approach is scientifically sound and consistent with the protection of aquatic life. I do, however, have some specific significant comments for EPA to consider which I list below.	Thank you for your comment.	No edits needed
Reviewer 4	Page 15: EPA concludes that most changes in Cd toxicity can be explained by changes in hardness and therefore incorporation of the BLM into this revision is not necessary. I strongly disagree with this statement. Every study I'm aware of in which a range of DOC and pH have been measured has shown that these parameters strongly influence Cd toxicity. Just because the majority of laboratory studies are conducted in laboratory waters with low DOC and do not measure dissolved organic carbon (DOC), does not provide a valid rationale for not using the BLM (biotic ligand model). Obviously, in the natural environment, DOC varies widely. I would think the objective of the criteria is to ensure that they are protective/predictive of toxicity in the natural environment, not in artificial laboratory waters.	EPA revised the text to indicate that hardness is a critical factor in determining toxicity, and additional water quality parameters such as DOC, alkalinity, and pH may also influence cadmium toxicity. As the external peer reviewer noted, the objective of the criteria is to ensure that they are protective and predictive of toxicity in the natural environment. The addition of consideration of DOC would generally yield higher criteria values. Thus the focus on hardness only in this draft is expected to be protective. The EPA may consider the applicability of the BLM including parameters such as DOC in future revisions of the cadmium criteria. Criteria were derived considering lab water-based exposures using procedures that are consistent with the 1985 Guidelines. Additional discussion has been added to address the uncertainty of using lab-based tests to determine safe field concentrations and the importance of dietary exposures to this faunal group. In addition, generally good agreement has been reported for microcosm studies/whole effluent toxicity test results with corresponding field observed effects (Clements and Kiffney 1996; Clements et al. 2002; Norberg-King 1986). Mebane	Section 2.3.1 Section 2.5 Section 5.1.3

		(2006) compared chronic criterion values and apparent effects values from ecosystem studies and field surveys and concluded that the data showed mostly good agreement between the laboratory-based predictions and effects observed in the field surveys or ecosystem experiments.	
Reviewer 4	Page 34: Following up on the previous comment regarding not using the BLM, why did EPA only consider a multiple linear regression with alkalinity? Why not pH and/or DOC? It is quite possible that pH autocorrelates with hardness as well given this is the case for most artificial laboratory waters (though not as consistent for natural waters), but there will not be an autocorrelation with DOC. This is a really important water quality parameter that EPA is ignoring.	Text relating directly to alkalinity was removed from the document and replaced with the text discussed in the previous response to comment. EPA notes that integrating DOC into the analysis would be expected in most cases to make the criteria less stringent. Thus, while recognizing the need to consider applicability of the BLM in future cadmium criteria updates, it is notable that the inclusion of DOC in the BLM approach will likely not make the criteria more stringent or conservative.	Section 2.3.1 Section 2.5 Section 5.1.3
Reviewer 4	Page 50-51: Is the study by Voyer et al. (1974), the only study where the effects of salinity on Cd toxicity was not consistent or are there multiple studies with this problem? If it's only this one study, it's not clear why the general trend would be ignored. I don't think EPA would ignore the hardness relationship in freshwater if only a single study was inconsistent with the general trend. It is a concern that there is an obvious and significant salinity effect for the *Neomysis integer* data (p. 51), which is one of the four taxa used for the criteria derivation, and yet this obvious effect is ignored and the geometric mean is used to develop the species mean acute values (SMAV). Does EPA consider a test performed at a salinity of 1 ppt to be a marine test?	Based on the peer reviewer's comments, additional analysis of the relationship between salinity and cadmium toxicity was conducted. As discussed in a previous comment, text has been added detailing why a salinity normalization approach was not used in the criteria development. A salinity-toxicity trend could not be definitively characterized and a mathematical relationship could not be described to define the dependency. EPA will continue to use the 1 ppt as the lowest salinity level for a saltwater test, consistent with the development of estuarine/marine criteria, which is applicable to the broad range of salinities characterized by these habitats. This salinity is also consistent with Mitsch and Gosselink (1986) who classify a waterbody with a salinity of 0.5-5.0 ppt as oligohaline. Note that for the salinity in the 1ppt *Morone* exposure, the conductance in this experiment was 1,600 uS/cm at 25C. This was approximately three times the conductance compared to fresh hard water. Mitsch, W.J. and J.G. Gosselink. 1986. *Wetlands.* Van	Section 2.3.1 Section 5.4.1

		Nostrand Reinhold, New York. 539 pp.	
Reviewer 5	Unfortunately some aspects of the document lead to answering both parts of the charge question 2 with answers of "no." I am only commenting on aspects which to me did not follow the available science, deviate from the principles of the 1985 "Guidelines" or otherwise have logical problems. While Stephan et al. (1985) Guidelines for derivation of aquatic life criteria are 30 years old and aspects of the science have progressed such that some details may not fit, they include solid principals that should continue to guide the approach. Key among Stephan et al. guiding concepts is from their p. 3: "*The guidelines were intended to provide the same level of protection as would an (infeasible) approach of conducting field tests on a wide variety of unpolluted bodies of water, adding various amounts of the material to each body of water in order to determine the highest concentration that would not cause any unacceptable long-term or short-term effects on the aquatic organisms or their uses*." Further (p. 10), *These National Guidelines have been developed on the theory that effects which occur on a species in appropriate laboratory tests will generally occur on the same species in comparable field situations. All North American bodies of water and resident aquatic species and their uses are meant to be taken into account*." Not bodies of water for which conditions are optimal – all bodies of water. Thus, a key concept behind the logic of criteria derivation is that criteria be suitable for diverse, natural water bodies, and laboratory data should attempt to encompass comparable field situations. The draft document instead moves towards a very different concept of only using data from an idealized aquaculture setting, without regard to whether the species occurs in the wild in waters with "suboptimal" conditions.	We concur that an objective of the 1985 Guidelines is to provide for the development of criteria that are applicable to a variety of field conditions. The testing procedures must, however, be conducted with organisms that are determined to be fundamentally healthy and with tests that meet with a consistent set of standards in order to evaluate test acceptability and develop criteria that are not impacted by testing artifacts and that are applicable on a national basis. This approach is consistent with internationally-recognized and broadly applied approaches for developing effects analyses for toxicants, relying on such reproducible laboratory data because they are designed to be as free from confounding influences as possible, in order to permit for robust, unconfounded consideration of risk for a given chemical, and relative risk across chemicals. States, tribes, and other end users can then consider site-specific conditions and variables in the development of standards that are applicable to their specific end use, such as the application to a particular water body or region. A further discussion of uncertainty regarding differences between laboratory and field conditions and implications for criteria has been added to the document.	Section 2.5 Section 5.1.3
Reviewer 5	Drilling down on Hyalella Most fundamentally, by throwing out all long-term test endpoints for the most sensitive genus (Hyalella) this	In addition to the response to the previous comment, additional text has been added to further detail the decision process that was used, based on the recently-completed	Section 2.5 Section 5.1.3 Section 5.2.1

	document strays from a guiding principle of the Guidelines that criteria are to protect diverse natural waters. Criteria are indeed developed using laboratory data, but they are not intended to apply to laboratory waters; they are intended to apply to natural waters. This disconnect between laboratory-based derivation of numeric water quality criteria and application to natural waters has repeatedly debated in the literature, with me chiming in specifically with cadmium (Mebane 2010). In essence, optimal aquaculture conditions are defined for culturing *Hyalella azteca*, and chronic tests in which less than 15 mg/L chloride was present in dilution waters, or control growth, survival, and reproduction did not meet expectations. These were control growth (≥0.35 mg at 28 days and ≥0.5 mg at 42 days), survival (80% at 42d) and reproduction (≥6 per young). No explanation was found in the document why researchers were tasked to drill down on Hyalella, as any commonly used test organism could have been similarly scrutinized. Absent explanation, the inference is that Hyalella must have been chosen because it was the most sensitive organism, and there was a desire to exclude data if this heightened sensitivity could be shown to be an artifact of stressful laboratory culture conditions. In essence this logic requires the following implicit assumptions. Since only Hyalella data obtained from laboratory test waters >15 mg/L are to be used for criteria development, it follows that: In ambient waters, Hyalella (and presumably other freshwater amphipods) are only expected to occur in waters with >15 mg/L chloride; Alternatively if Hyalella do in fact occur in waters with lower chloride concentrations, the criteria are only intended to apply to waters with >15 mg/L. Chloride is an important factor affecting the toxicity of cadmium to Hyalella (and presumably other related but less well studied amphipods or freshwater crustaceans). If so, then it follows that: Chloride should be included in the criteria derivation and	evaluation, to determine which *Hyalella* tests were included in the evaluation. The basic premise behind the selection of specific *Hyalella* tests, based on the consideration of test conditions, is that in order to develop robust comparative toxicity tests, animal husbandry conditions should be optimal and provide for low control mortality and optimal control growth to decrease control noise, increase the ability to capture low level effects, and thus understand the implications of introducing a toxicant into the system even at low levels. EPA developed this test condition/husbandry analysis for *Hyalella* after repeatedly observing extremely high variability in *Hyalella* test results for the same compound under different lab/husbandry conditions (e.g., chloride concentrations in test water) and considering less than optimal control survival, growth and reproduction. These analyses led to the determination of conditions under which repeatable results could be obtained by minimizing interfering confounders, such as water chemistry and diet. These analyses were <u>not</u> developed to exclude sensitive tests. EPA's analyses are developed with the goal of generating high quality and scientifically defensible predictions of concentrations, that if not exceeded beyond the specified frequency and duration, will be protective of aquatic life.	

	factored into the criteria. Per the Guidelines (p32), "when enough data are available to show that the chronic toxicity is similarly related to a water quality characteristic, the relationship should be taken into account …. If two or more factors affect toxicity, multiple regression analysis should be used." Alternatively, while not specifically mentioned in the guidance, if data were insufficient for the covariance or multiple regression analyses endorsed, it would seem reasonable to establish different criteria in brackets, such as waters ≤15 mg/L chloride or >15 mg/L chloride. Alternatively, if chloride is not an important factor affecting, then there is no reason to factor it into the criteria development. However, Appendix K does not address the question of whether chloride is a factor affecting cadmium toxicity, all that has been established is that Hyalella growth and reproductive output is greatest in waters with chloride >15 mg/L. This is not unexpected. Freshwater environments usually have an osmolarity far less than blood plasma, and energy requirements to maintain hydromineral balance increase in more dilute waters (e.g., Wendelaar Bonga and Lock 2008). Fish in dilute waters don't grow well either. For instance, about 80% of the restaurant/retail rainbow trout sold in the United States come from a 30 mile stretch known as the Thousand Springs area of southern Idaho. There the constant chloride of about 20 mg/L, hardness of about 180 mg/L and temperature of 15°C provide optimal energy conversions and growth per unit feed. It would follow just as logically that only rainbow trout data that were generated from waters with chloride >15 mg/L or so should be used, because that optimizes growth? Why would it not follow that only acute data in which organisms were fed should be used, because starvation stresses organisms? This seems to be internally inconsistent logic.		
Reviewer 5	The reason why Appendix K was requested was never stated.	The basic premise behind the selection of specific *Hyalella*	Section 2.5

	It should be. I assume the reason must be a presumption that if organisms do not grow and reproduce at high rates, then they will "too sensitive" or not represent responses expected in natural conditions. It is not obvious that this is the case. McNulty et al. (1999) showed that starved amphipods exposed to low levels of cadmium survived better than controls. However, even if optimal diets do produce higher (less sensitive) growth and reproduction effects with Cd and Hyalella, the universal use of optimal diets could lead to underestimation of the toxicity risks experienced by wild populations, which may experience limited food availability. In the wild, organisms don't live in optimal conditions. Even in the center of their ranges, conditions are seldom optimal all of the time. Organisms also live in marginal conditions, for they tend to expand their ranges to the limits of their physiological tolerances. See for example France's (1996) description of Hyalella living on the margins of lakes with tolerable mineral content (France 1996). Similarly, Gibbons and Mackie (1991) showed that increasing reproductive output of H. azteca was associated with increasing sulfate, calcium hardness, sediment particle size, conductivity, alkalinity, seston, and the organic matter of the fine sediment. This consistent with Appendix K, but begs the question, what are effects of Cd in these suboptimal waters? Why assume that if Cd criteria are needed, they should only be developed from exposures in high hardness, but then blindly extrapolate results to low chloride, low hardness conditions using tests with other organisms? This is further logical problem with Appendix K's rationale – as noted in appendix K, waters with hardness less than 80 mg/L tend to have chloride less than 10 mg/L. Does the hardness-toxicity relation predict safe conditions for Hyalella at low hardness? No way to know.	tests, based on the consideration of test conditions, is that in order to develop robust comparative sensitivity analyses, animal husbandry conditions should be optimal and provide for low control mortality and optimal control growth to decrease control noise, increase the ability to capture low level effects, and thus understand the implications of introducing a toxicant into the system even at low levels. EPA developed this test condition/husbandry analysis for *Hyalella* after repeatedly observing extremely high variability in *Hyalella* test results for the same compound under different lab/husbandry conditions (e.g., chloride concentrations in test water) and considering less than optimal control survival, growth and reproduction. These analyses led to the determination of conditions under which repeatable results could be obtained by minimizing interfering confounders, such as water chemistry and diet. These analyses were <u>not</u> developed to exclude sensitive tests. EPA's analyses are developed with the goal of generating high quality and scientifically defensible predictions of concentrations that if not exceeded beyond the specified frequency and duration will be protective of aquatic life. We concur that an objective of the 1985 Guidelines is to provide for the development of criteria that are applicable to a variety of field conditions. The testing procedures must, however, be conducted with organisms that are determined to be fundamentally healthy and with tests that meet with a consistent set of standards in order to evaluate test acceptability and develop criteria that are not impacted by testing artifacts and that are applicable on a national basis.	Section 5.1.3 Section 5.2.1 Section 5.6.1
Reviewer 5	I've poked around a bit the literature on Hyalella life histories under different environmental stresses in an effort to include extrapolate organism-level effects of Cd to potential population-level effects (Mebane 2010). While by no means	The basic premise behind the selection of specific *Hyalella* tests, based on the consideration of test conditions, is that in order to develop robust comparative sensitivity analyses, animal husbandry conditions should be optimal and provide	Section 2.5 Section 5.1.3 Section 5.2.1 Section 5.6.1

	exhaustive, and by now a bit dated, this leads to some other thoughts on the expected control survival, growth, and reproduction in long term tests in Appendix K. With control survival, in at least some wild populations, I estimated half-month survival rates for juveniles of about 0.9, or close to a 5% decline per week (Mebane 2010, Table II). This is higher than the 2-3% noted in Appendix K, and suggests that in the wild, survival to 42-days would likely be less than 80%. With regards to growth, while some wild populations grew as much as those in the laboratory settings discussed in Appendix (>0.5 mg at sexual maturity), this cannot be assumed in all natural waters. Cooper (1965) reported average dry weights of adults Hyalella were 0.2 mg in a population in a warm, shallow lake in Michigan. Gibbons and Mackie (1991) reported mean weights of Hyalella at maturity were only 0.1 mg, and weights of all Hyalella were only 0.3 mg. Thus the 0.35 at day 28 and 0.5 mg at day 42 may be higher than that expected in some natural settings. Gibbons and Mackie (1991) reported ranges of brood per female ranged from 6 – 15, which is consistent with appendix K. However, Strong (1972), his fig 4, showed sometimes natural brook sizes may be as low as 3 per female. In sum, the logical problems of how Appendix K's analyses are used in the document are analogous to the metaphor of not seeing the forest because of all the trees. Some trees were examined in great detail (lab performance of Hyalella) but it misses the point that the comparisons of acceptable conditions should be again performance in the wild.	for low control mortality and optimal control growth to decrease control noise, increase the ability to capture low level effects, and thus understand the implications of introducing a toxicant into the system even at low levels. EPA developed this test condition/husbandry analysis for *Hyalella* after repeatedly observing extremely high variability in *Hyalella* test results for the same compound under different lab/husbandry conditions (e.g., chloride concentrations in test water) and considering less than optimal control survival, growth and reproduction. These analyses led to the determination of conditions under which repeatable results could be obtained by minimizing interfering confounders, such as water chemistry and diet. These analyses were <u>not</u> developed to exclude sensitive tests. EPA's analyses are developed with the goal of generating high quality and scientifically defensible predictions of concentrations that if not exceeded beyond the specified frequency and duration will be protective of aquatic life. We concur that an objective of the 1985 Guidelines is to provide for the development of criteria that are applicable to a variety of field conditions. The testing procedures must, however, be conducted with organisms that are determined to be fundamentally healthy and with tests that meet with a consistent set of standards in order to evaluate test acceptability and develop criteria that are not impacted by testing artifacts and that are applicable on a national basis.	
Reviewer 5	Other items: Problem formulation: It is germane to note that in natural waters, Cd is always in association with Zn, usually at about mass ratios of 1:200 (Wanty et al. 2009).	This information was added to Section 2.1 of the document.	Section 2.1
Reviewer 5	p. 12, I was not quoted quite accurately. "Mebane (2014 2006) concluded that, although there were not adequate data to establish acceptable tissue effect concentrations for aquatic life, cadmium is unlikely to accumulate in tissue to levels that	Text was added as suggested and the citation was fixed.	References and various locations in document

	would result in adverse effects to aquatic invertebrates or fish, at calculated chronic criterion concentrations, which were lower than that chronic criterion concentration derived here. " This report is variously cited as Mebane (2006), Mebane (2010), or Mebane (2014). The suggested citation is, "*Mebane, C.A. 2006. Cadmium risks to freshwater life: derivation and validation of low-effect criteria values using laboratory and field studies. U.S. Geological Survey Scientific Investigation Report 2006-5245 (2010 rev.). http://pubs.usgs.gov/sir/2006/5245/.*" The 2010 revision only corrected minor mistakes, and did not include any updated literature reviews.		Section 2.3 Section 5.6.1
Reviewer 5	p. 28, the approach of requiring data used in the hardness-toxicity regressions to have a 3X spread and 100 mg/L absolute difference between the highest and lowest value was indeed used in the 2001 version, but was not really presented as policy. In contrast, my colleagues and I found that hardness-toxicity relations were more reliable from test series that concurrently tested the same cohort of organisms in waters with different hardness, than were ad hoc collections of found data tested under different conditions at different hardness levels (Mebane et al. 2012). Where available, giving concurrent test series data obtained at different hardnesses precedence over general hardness-toxicity compilations would be warranted.	The approach of requiring data used in the hardness-toxicity regressions to have a 3X spread and 100 mg/L absolute difference between the highest and lowest value was established when updating the cadmium document in 2001. This practice has been followed for all subsequent criteria document updates because it was found that the variability associated with different test conditions that are associated with multiple studies can sometimes be so great that it masks the hardness/toxicity relationship. Data for each species are first reviewed to determine if they are potentially suitable for use in the hardness-toxicity evaluation. The data are initially considered regardless of source/test condition (laboratory, dilution water, temperature, etc.). However, if the hardness/toxicity data are widely scattered, we then attempt to decrease uncertainty introduced by the differing test conditions by focusing on those studies specifically evaluating the toxicity relationship. In addition, studies are excluded when only a single acute toxicity value was available and where multiple tests were conducted at the same hardness. When different life stages were used at test initiation, only data for the same life stage is evaluated. The end result is that the most defensible data are used to develop	No edits

		the hardness-toxicity slope.	

2.3 CHARGE QUESTION 3

3. Please comment on the data used to derive the revised criteria, including data adequacy/comprehensiveness, and the appropriateness of the data selected and/or excluded from the derivation of the draft criteria. Is the data used correctly for the intended purpose? Are there other relevant data that you are aware of that should be included? If so, please provide the data along with supporting information.

Reviewer	External Peer Reviewer Comments Regarding Charge Question 3	EPA Response	Revision Location in 2015 Draft Cadmium Criteria Document
Reviewer 1	As noted above, the author chose to ignore many relevant studies that did not conform with standard EPA toxicity protocols. But the problem is that these protocols basically ignore the fact that animals eat, hardly a realistic scenario and are too simplistic in looking only at growth and mortality. Typically, the test organisms are exposed to dissolved Cd at varying concentrations, but in the absence of food. Occasionally, some artificial food (fish flakes or the like) is presented once every several days (sometimes never!) to keep the animals alive. But these studies are hardly representative of what happens in natural waters.	Studies that were determined not to be acceptable were presented in Appendix J, along with a rationale for their exclusion. However, the exclusion of food in acute tests is standard practice in EPA, ASTM and internationally-harmonized toxicity test protocols. This is based on the potential for food to alter the exposure concentration and/or bioavailability of the chemical. This approach is consistent with procedures stated on page 14 of the 1985 Guidelines: "Except for test with saltwater annelids and mysids, results of acute tests during which the test organisms were fed should not be used, unless data indicate that the food did not affect the toxicity of the test material".	No edits needed.
Reviewer 2	The use of additional species for SSD reduced uncertainty and greatly improved criteria assessments for freshwater. The QA evaluations of data usefulness was adequate and the data selected for the acute responses was correctly used for the intended purpose. The mechanistic assumption that adverse effects are primarily related to calcium uptake at the gill, is accurate for acute effects. Consequently, the data used for derivation of the criteria for acute effects is valid.	Thank you for your comment.	No edits needed.

Reviewer 2	However, with regard to chronic effects, there are other targets once absorption of cadmium occurs, particularly the kidney, brain and gonad. In addition to specific interactions with signaling proteins, Cd clearly binds sulfhydral groups of proteins within targets disrupting cellular maintenance. The latter two tissue targets above are likely involved in the reproductive effects observed with chronic exposures. Cd clearly disrupts the Hypothalmic Pituitary Gonadal axis and gonadal function in fish (Vetillard, and Bailhache 2005). It reduces vitellogenin in females and accumulates in kidney upon chronic exposures either via diet or water (Szczerbik et al. 2006; Thomann et al. 1997). It is understood that tissue data from these organs are limited, but studies that have these data, or the fact that these data are limited should be discussion points of the uncertainty analysis. Clearly, discussions of uncertainty regarding accumulation are needed, particularly in light of limited data for chronic effects in estuarine/marine organism. The statement "Aquatic organisms are considered to be more susceptible to cadmium from direct aqueous exposure than through bioaccumulation and the development of criteria protective of direct exposure effects are considered more applicable to the development of criteria for aquatic life" is clearly biased toward acute toxicity and should be re-visited with particular emphasis on reproductive effects of cadmium which likely result from accumulation and not direct exposure.	EPA recognizes the difficulty in characterizing dietary exposure and establishing critical tissue effects thresholds associated with bioaccumulated metals. The information provided regarding tissue targets has been added to the Uncertainty section along with additional discussion about limitations in the organ data. Text has been added to discuss these points and incorporate the work of other researchers, such as Mebane (2006), who discuss cadmium bioaccumulation and dietary exposure in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and toxicological effect, and an acceptable tissue effect concentration cannot be defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	Section 5.6.1

Reviewer 2	With regard to reproduction, it is unclear what endpoint data is being used to determine the effect values in the Appendices. Tests are provided in terms of exposure duration, but it is unclear whether growth, survival or reproduction is being utilized as the endpoint. Again, given the potential for reproductive effects upon chronic exposure, reproduction would be expected to be the most sensitive endpoint. If other endpoints were used then the uncertainties inherent to these endpoints should be discussed. Clearly growth and survival effects have likely difference mechanisms and targets than that of reproduction.	The most sensitive acceptable endpoint is used for each study. The endpoint for each exposure concentration was added for each study in the table.	Appendix C
Reviewer 2	It is also significantly disappointing that data from the same 2 species in 1980s are still the only two species being used to derive the 2015 values. In addition, it is puzzling how criteria values can be raised for estuarine/marine organisms when the same degree of uncertainty exists (only 2 species) in each year criteria were assessed. To add in data from freshwater organisms for ACR estimates *increases* uncertainty and does not reduce it. Therefore, the 2001 value should stay as is, or be reduced because of the uncertainty associated with its derivation.	Additional acceptable estuarine/marine chronic data were not found based on an extensive literature search that was conducted in 2014. The CCC was calculated using the saltwater FAV and FACR as recommended in the 1985 Guidelines. The use of a freshwater ACR to derive estuarine/ marine values is described as an acceptable approach in the 1985 Guidelines, and was used in the draft criterion document reviewed by the external peer reviewers. Based on the peer reviewer comment, the estuarine/marine ACR approach was re-examined and revised for the 2015 draft proposal for public comment. The revised FACR incorporates data for seven genus-level ACRs and was derived using data for marine species and a diversity of freshwater species, many of which have taxonomically-related marine species. ACRs used to derive the FACR incorporate data for five freshwater fish species, three freshwater invertebrate species, and two acutely sensitive estuarine/marine mysids.	Section 2.7.3 Section 4.4.2 Section 5.5.1

Reviewer 3	Practically all relevant work related to bioaccumulated Cd and the importance of dietary exposures is ignored. (see (Barata et al. 2002, Barata et al. 2002, Buchwalter et al. 2008, Cain et al. 2004, Croteau et al. 2003, Hare et al. 2001, Hare et al. 2003, Irving et al. 2003, Klaassen et al. 1999, Luoma and Rainbow 2005, Luoma et al. 2009, Luoma and Carter 1991, Martin et al. 2007, Timmermans et al. 1992, Wallace et al. 2003, Xie et al. 2010, Xie and Buchwalter 2011, Xie et al. 2008) for some examples)	The referenced materials were evaluated and added, as applicable, to the bioaccumulation uncertainty section.	Section 5.6.1
Reviewer 3	I suspect that there are other reviewers who can comment more directly on the issues with *Hyalella* data, so I will refrain from doing so here.	Thank you for your comment.	No edits needed.
Reviewer 4	Overall, I found the data used by EPA to derive the criteria to be comprehensive and generally sound. There are a few specific data where I have concerns that EPA should consider as described below.	Thank you for your comment.	No edits needed.
Reviewer 4	Page 51: I'm very concerned that EPA is still allowing studies in which test concentrations were unmeasured as being acceptable for WQC derivation. This is particularly concerning when they are for one of the four taxa used to calculate the criteria. In my opinion, these studies should not be included.	The use of unmeasured acute test study results is an acceptable approach in the 1985 Guidelines under specific conditions. The lack of measured exposure concentrations in an acute toxicity test does not invalidate the results if there is a demonstration that the material tested is stable during the testing period. Only if there were observed solubility problems (e.g., precipitant present) would the data be suspect and therefore potentially not acceptable.	No edits needed.

Reviewer 4	Page 68: I agree with EPA's use of freshwater ACRs to supplement the limited marine ACRs for the purpose of deriving a final marine ACR. However, I question whether use of the ACR for *Lampsilis siliquoidea* is appropriate. There are obviously a number of factors that influence the ACR, but a major factor is the life history of the organism and the life stage selected for the acute toxicity test used to derive the ACR. It seems to me that freshwater mussels have a unique life history with no real analog in marine systems (marine bivalves have a different life history). Consequently, use of this of the ACR for this species to derive a marine ACR seems inappropriate. I think use of an ACR for daphnids would be more appropriate and representative of the life history of the most acutely sensitive taxa in marine systems, the copepod *Tirgriopus*.	Based on peer reviewer comments, calculation of the FACR was revised and does not include *Lampsilis*. The revised FACR incorporated data for seven genus-level ACRs and was derived from data for marine species and a diversity of freshwater species, many of which also have taxonomically-related marine species. ACRs used to derive the FACR incorporate data for five freshwater fish species, three freshwater invertebrate species (including applicable data for daphnids), and two acutely sensitive estuarine/marine mysids.	Section 2.7.3 Section 4.4.2 Section 5.5.1 Section 5.5.2
Reviewer 4	Table 17: Why is the pH 6.0 test for *H. azteca* excluded? This is within the range of test pH values (6.0-9.0) normally considered by EPA. Additionally, earlier in the document it was stated that hardness was the only water quality parameter that mattered for normalizing Cd toxicity data. I disagree with that statement, but if EPA is going to argue other water quality parameters are not important, then I don't see how it can then exclude data for this reason.	In addition to the pH being below the level accepted by EPA for tests (6.5-9.0), Br and Cl^- concentrations were not provided and the dilution water was comprised of well water that was significantly diluted from a hardness of 380 mg/L to 15.3 mg/L (Mackie 1989). The *Hyalella* memo found in Appendix K of the draft criteria document states that "Natural waters with hardness less than 80 mg/L typically have <10 mg Cl/L". The rationale for the exclusion of this study from the criteria derivation was clarified in the document table.	Table 17

Reviewer 4	Table 18: I agree with EPA's re-evaluation of the *Hyalella* data and their application of water quality and performance criteria for test acceptability. However, I'm concerned about the study EPA retained for purposes of criteria derivation for several reasons. First, I do not believe use of a 10-d survival endpoint constitutes a chronic study as defined in Stephan et al. (1985). EPA has excluded a number of other studies from use in criteria derivation for this reason (e.g., the 21-d survival study on the sea starlet anemone, p. 81) in this document that creates a major internal inconsistency. Having said that, it could be argued that inclusion of this sub-chronic data is warranted given that it is the lowest toxicity value in the data set and exclusion of the data would be non-conservative in terms of environmental protection (as opposed to including sub-chronic data for insensitive species). However, using this logic why would the 7-d survival/growth data with the fountain darter then be excluded?	In response to peer reviewers' comments, a further examination of this issue was conducted. Thus, after further evaluation, the full-life cycle study by Ingersoll and Kemble (2001) was found to satisfy the acceptability criteria for *H. azteca* and was used to replace the 10d study used in the previous draft of the document. This change is based on consultation with the study author, where it was determined that techniques used to measure length data are likely to more accurately reflect growth than the originally-reported direct weight measurements. Since the original study was conducted, this laboratory has developed a robust empirical relationship between amphipod length and weight. Applying the formula, the 28-d average control length translates into a weight that is above the minimum control performance values listed in Appendix K of the draft criteria document. The average control reproduction for this study also met minimum performance values. Although the feeding rate used in this test was below that recommended for *H. azteca*, the finding that control organisms met the performance criteria of tests using a higher feeding rate supports retaining these data for use in deriving the AWQC.	Section 3.1.2 Section 5.2.1
Reviewer 4	My second concern is whether the sensitivity of *H. azteca* is real? Given that these 10-d data come from a 42-d study that fails to meet control performance criteria, how does EPA know that these animals weren't already stressed at 10 d and inappropriately sensitive? Given both the duration and performance issues associated with these data, in my opinion they should not be used for WQC derivation. However, I strongly encourage EPA to conduct a 28- or 42-d *Hyalella* study that meets the necessary performance criteria. Finally, after Table 18, EPA has descriptions of each of the chronic *H. azteca* studies and rationale for their rejection but did not include a description of the Ingersoll and Kemble study that was accepted and the rationale for use of the 10-d survival endpoint. This should be added to the document.	Please see response to previous comment. As indicated in the response, the full-life cycle study by Ingersoll and Kemble (2001) was found to satisfy the acceptability criteria for *H. azteca* and was used to replace the 10d study used in the previous draft of the document. The Agency is interested in obtaining information regarding new toxicity tests on *H. azteca* as noted in the Federal Register Notice to be issued announcing the availability of the 2015 draft cadmium criteria document for public comment.	Section 3.1.2 Section 5.2.1

Reviewer 5	As noted in the response above, the exclusion of most Hyalella data is doubtfully justifiable, because the criteria for doing so are questionable. However, even with these Appendix K criteria as they are, the Ingersoll and Kemble data reproductive data should not have been excluded. The 42d reproductive endpoint from that test met the Appendix K criteria for control survival and brood size (6.35 per female). The 28 day endpoint was presumably excluded because of low growth as weight. However, the organisms were not weighed, but rather lengths were measured and weights were inferred from lengths. Regardless, by the stated logic, it would follow to exclude the 28-day endpoint with low (estimated) weight. But to then pick an acute survival endpoint (10-day) instead of the 42-day reproductive endpoint is inexplicable. The entry for this test in Table 2 is misleading. Saying the test was a life cycle test, but then using an acute endpoint, is misleading. I estimated the EC20 for reduced reproduction to be about 1.2 µg/L using logistic regression, or the MATC (geomean of LOEC and NOEC) would be 0.98 µg/L.	In response to peer reviewers' comments, a further examination of this issue was conducted. Thus, after further evaluation, the full-life cycle study by Ingersoll and Kemble (2001) was found to satisfy the acceptability criteria for *H. azteca* and was used to replace the 10d study used in the previous draft of the document. This change is based on consultation with the study author, where it was determined that techniques used to measure length data are likely to more accurately reflect growth than the originally-reported direct weight measurements. Since the original study was conducted, this laboratory has developed a robust empirical relationship between amphipod length and weight. Applying the formula, the 28-d average control length translates into a weight that is above the minimum control performance values listed in Appendix K of the draft criteria document. The average control reproduction for this study also met minimum performance values. Although the feeding rate used in this test was below that recommended for *H. azteca*, the finding that control organisms met the performance criteria of tests using a higher feeding rate supports retaining these data for use in deriving the AWQC.	Section 3.1.2 Section 5.2.1
Reviewer 5	Other specific points on data used or not used. <u>Durations of tests</u> If 30-day tests with salmonids that started with fry consistently yield more sensitive results than 60-day tests that started with eggs or embryos, why ignore all the shorter, more sensitive tests. The Guidance counsels to beware of tests in which acclimation probably occurred during resistant states. Chapman (1985) recently described this problem. It would make more sense to exclude the less sensitive data, rather exclude the more sensitive data.	Use of the life cycle (LC) tests over the early life stage (ELS) tests in the draft reviewed by the external peer reviewers was consistent with the 1985 Guidelines. It was noted that there was no consistent pattern of early life stage tests being more sensitive than life cycle tests for salmonids Subsequently, based upon peer reviewer comments, use of sensitive salmonid tests was reconsidered and changes in the approach were made for the 2015 draft criteria. Specifically, ELS tests were used to calculate the revised SMCV in instances where they were more sensitive than the LC tests (e.g., *Salmo trutta*).	Section 3.1.2 Section 5.2.2 Appendix C

Reviewer 5	Likewise with Mottled Sculpin, there's doubtfully anything special about 28-day exposures over 21-day exposures. Besser et al. (2007) ran two tests, one 28-day and one 21-day test. The 28-day was less sensitive, and it was used with the other ignored. There is no established ASTM protocol for Mottled Sculpin, and the ASTM (1998) mention of "28 to 120-day (depending on species) continuous exposure" tests for early-life stage tests refers back to their species-specific appendices.	The SMCV/GMCV for the most sensitive fish species, *Cottus bairdii*, is from the results of one 28-d ELS test (Besser et al. 2007). The other study reported in the same paper, a 21-d ELS study, was not used quantitatively for the criteria derivation because there is a lack of guidance on the most appropriate duration for ELS tests with this species. U.S. EPA and ASTM guidance implies that ELS tests should last at least 28 days, so these data were not added to Appendix C. However, it is noteworthy that incorporating these data would only change the CCC slightly; the SMCV would change from 1.721 to 1.470 µg/L, and the criteria would only change by one-hundredth of a microgram, from 0.80 to 0.79 µg/L total cadmium.	Section 5.2.2
Reviewer 5	Other data (Calfee et al. 2014) and (Wang et al. 2014) report acute and chronic data with White Sturgeon and Rainbow Trout. The same data are reported in Environmental Toxicology and Chemistry, but Wang is paywalled, so I would use the open access USGS report version.	The cited papers were reviewed and the additional acceptable data were added to the appropriate tables and appendices.	Appendix A Appendix C Table 7 Table 20 Sections 5.1 Section 5.8.1
Reviewer 5	An acute test with Mottled Sculpin, (*Cottus bairdi*) and Cd was attributed to Mebane et al. (2012). We tested Shorthead Sculpin, *Cottus confusus*.	This was an error. The species name will be corrected, as appropriate.	Various locations

2.4 CHARGE QUESTION 4

4. Are the derived criteria appropriately protective of listed species and commercially and recreationally important species, particularly as the criteria relates to salmonids?

Reviewer	External Peer Reviewer Comments Regarding Charge Question 4	EPA Response	Revision Location in 2015 Draft Cadmium Criteria Document
Reviewer 1	I agree with the author that marine animals are less at risk than freshwater animals, and this is primarily due to the strong chloro-complexation of Cd in seawater, thereby reducing the bioavailability of Cd. Consequently, marine bioconcentration factors are often 1-2 orders of magnitude higher in freshwater.	Thank you for your comment.	No edits needed.
Reviewer 1	I also agree that plants (e.g., phytoplankton) are less sensitive to Cd than animals, and thus it is appropriate to focus on the animals.	Thank you for your comment.	No edits needed.

Reviewer 1	I think that the criteria that the author generated for dissolved Cd have taken into consideration many of the key issues influencing this (e.g., water hardness) are probably ok, but by missing the effects of dietary Cd, the report is missing a large part of the overall story. This is not to suggest that ambient Cd concentrations are unsafe for animals, but the derived criteria are probably over-estimates of the safe levels of Cd.	Text has been added to discuss dietary exposure and incorporate the work of other researchers, such as Mebane (2006), who discuss cadmium bioaccumulation and dietary exposure in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and toxicological effect, and an acceptable tissue effect concentration cannot be defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	Section 5.6.1
Reviewer 1	Another complicating issue is the influence of dissolved organic carbon and its effect on Cd bioavailability. Thus, expressing Cd toxicity as a function of body burden is appropriate; the caveats associated with this approach have been appropriately discussed in the report.	EPA revised the text to indicate that in addition to hardness, which is a critical factor in determining toxicity, other water quality parameters such as DOC, alkalinity, and pH may also influence cadmium toxicity. EPA notes that integrating DOC into the analysis would be expected in most cases to make the criteria less stringent. Thus, while recognizing the need to consider the applicability of the BLM in future cadmium criteria updates, which would incorporate DOC, the inclusion of DOC in a BLM would be unlikely to make the criteria more stringent or conservative.	Section 2.3.1 Section 2.5 Section 5.1.3

Reviewer 2	Salmonids are clearly one of the more sensitive species with regard to Cd toxicity. Not only are they very sensitive, they are commercially important, and possess several species that are listed as endangered and threatened in the US. The proposed criteria are appropriate for freshwater conditions since many of the studies used to derive the criteria focused on freshwater treatments to rainbow trout. However, only one study evaluated Cd toxicity in coho salmon smolts in saltwater conditions, and this was at nearly full seawater strength (28 ppth). Of concern is the fact that many salmonids including strains of *O. mykiss* (steelhead) are anadromous and often come in contact with Cd at lower salinities (5-15 ppth). While the agency should be applauded for normalizing toxicity to hardness to improve freshwater criteria, there is a critical need to understand the impacts of salinity on Cd toxicity particularly in anadromous salmonid species. Of additional concern is the lack of discussion of sublethal impacts of Cd particularly to olfaction (Williams and Gallagher 2013) which significantly alters return rates of salmon (Baldwin et al. 2009). Return metrics are population level endpoints that should supersede standard repro/survival/growth. These should also be topics of discussion with regard to uncertainty.	Additional acceptable estuarine/marine toxicity data were not available for salmonids. Additional text (and references) was added to the appropriate uncertainty sections to emphasize the absence of these data.	Section 5.4.1 Section 5.5.2
Reviewer 2	Lastly, the issue of climate change is largely missing from the document. Acidification (particularly with metal availability) and temperature issues are also likely to impact sensitive species (e.g. salmonids). Sea level rise will also cause saltwater intrusion into salmonid spawning habitats and affect "estuarine/marine" criteria. Evaluation of these stressors should be focal points for future criteria assessment particularly for salmonids. Overall, while the values for freshwater are likely safe for salmonids, the values for estuarine/marine are highly uncertain and deserve further evaluation.	Thank you for your comment. EPA revises the criteria documents based on the best available scientific information at the time of development and based on current conditions in the environment. Criteria documents are then periodically revised to incorporate the latest scientific information based on toxicity and consideration of applicable environmental conditions.	No edits

Reviewer 3	This seems to be the case if we assume that only aqueous exposures matter. Evidence for dietary toxicity is less compelling than for invertebrates, so for these fish species, the criteria are likely more protective for these species than they are for invertebrates.	EPA concurs with the reviewer about the difficulty of characterizing dietary exposure and establishing critical tissue effects thresholds for bioaccumulated metals. Text has been added to discuss dietary exposure and incorporate the work of other researchers, such as Mebane (2006), who discuss dietary exposure and cadmium bioaccumulation in detail and the uncertainties currently associated with its evaluation. In particular, text was added to detail how cadmium can bioaccumulate in aquatic organisms through multiple exposure routes including ingestion and direct exposure, and how total uptake depends on the cadmium concentration, exposure route and the duration of exposure. Text was also added to clarify that there does not appear to be a consistent relationship between body burden and toxicological effect, and an acceptable tissue effect concentration cannot be defined for aquatic life at this time. Bioaccumulation and effect level data that are available indicate that cadmium is unlikely to accumulate in tissue to levels that would result in adverse effects to aquatic invertebrates or fish at the calculated chronic criterion concentrations. For this reason, the evaluation of direct exposure effects to organisms via water is considered applicable to the development of criteria that is protective of aquatic life.	Section 5.6.1

Reviewer 4	Yes, I think the criteria as derived will be protective of salmonids. However, I'm concerned about the exclusion of the fountain darter data from the derivation. EPA argues that the acute data should be excluded because the test was fed and that the chronic data should be excluded because the study was only 7 d in duration (i.e., not true chronic). Generally, I agree with both of these decisions, but from my perspective, these rules are in place to prevent the inclusion of data indicating organisms are insensitive due to inappropriate test conditions (i.e., food reducing metal bioavailability, short test durations missing sensitive endpoints). However, this is not the case with the darter data, which indicate this species is very sensitive despite test conditions that would tend to reduce their sensitivity. EPA also seems to infer (p. 86) that the fountain darter data has limited applicability because this species has a limited distribution. However, the genus *Etheostoma* is widespread throughout central and eastern U.S. with a number of listed species at both the state and federal level. Hence these data a representative for a genus that is under considerable threat. Given this, I think it would be important to assess how inclusion of these data would impact derivation of the freshwater Cd WQC.	Text has been added to clarify that data eliminated were not used in criteria derivation because the test organisms were fed and the duration was too long for an acute test and too short for a true ELS test. EPA also added text indicating the genus *Etheostoma* is widespread, with some of species representing those of special concern. It is important that states evaluate the potential occurrence of these species when establishing site-specific standards.	Section 5.8.1 Section 5.8.2

Reviewer 4	Page 87: I don't think the statement that dividing the LC50 by two is expected to result in a concentration with effects no different than the control is correct. Dividing the LC50 by two will result in an "LC-low". I agree that across a range of species and toxicants, dividing by two equates to a values that approximates the NOEC. However, it does not equate to an LC0, which is inferred by this statement. Please clarify.	Dividing the FAV by a factor of two to derive a CMC is the standard approach used by the Agency to derive its 304(a) acute criterion recommendations, consistent with the 1985 Guidelines. The FAV is a statistical estimate of the 5th percentile of a set of LC50s. The LC50 is defined as the concentration that kills 50% of the exposed organisms. Thus, by definition, the FAV, as defined in the 1985 Guidelines, is a concentration that would be lethal to 50% of organisms with a sensitivity greater than 95% of genera. Since the FAV is a concentration that may affect 50 percent of the 5th percentile or 50 percent of a sensitive species, this value cannot be considered to be protective of that percentile or that species. Therefore, per the 1985 Guidelines, to derive the CMC EPA divides the FAV by a factor of 2 with the intention of defining a concentration that will not affect the majority of organisms. The rationale for adjusting the FAV to derive the CMC is explained in item 6 on page 17 of the 1985 Guidelines. The basis for this adjustment factor is an analysis of data from 219 acute toxicity tests showing that the mean concentration lethal to 0-10% of the test population was 0.44 times the LC50 or the LC50 divided by 2.27. The data and analysis on which the 2.27 value is based is described in the Federal Register on May 18, 1978 (43 FR 21506-21518). Best professional judgment was used to round the FAV "adjustment factor" of 2.27 to 2 in revisions of the Guidelines that occurred subsequent to the 1987 Federal Register notice. The use of the factor became final EPA guidance in the 1985 Guidelines.	Section 5.1.3

Reviewer 5	Not necessarily, although to definitively answer this would take a considerably more thorough review to determine than was presented in the document, or could be done independently in the time available. I note that NMFS (2012) in Oregon concluded the 2001 CMC of 2.0 µg/L could jeopardize some salmonids and that the CCC of 0.25 µg/L would not jeopardize listed salmonids under their prevue. Thus the draft 2015 criterion of 2.2 µg/L would presumably be a concern. Conversely, NMFS (2011) concurred with EPA that Idaho acute and chronic criteria of 1.34 and 0.55 µg/L respectively would not jeopardize listed anadromous salmonids. I did not attempt to reconcile the three documents. However, I think part of the discrepancies may be in the manner of analyses. In the draft document, data from long-term exposures to salmonids that began with sensitive fry life stage are excluded in favor of data from tests that began with eggs or alevins. While all fish have some life stage-sensitivity interaction, with at least salmonids sensitivity increases with size up to at least 0.4g ww, and maybe up to 1g or more (Hansen et al. 2002; Mebane et al. 2012). With other fish, the newly hatched stage may be more sensitive, or life events such as the onset of exogenous feeding may be related to a stressful and sensitive stage (Wang et al. 2014).	Use of the life cycle (LC) tests over the early life stage (ELS) tests is consistent with the 1985 Guidelines. Furthermore, there is no consistent pattern of early life stage tests being more sensitive than life cycle tests for salmonids However, to account for this discrepancy, ELS tests were used to calculate revised SMCV in instances where they were more sensitive than the LC tests (e.g., *Salmo trutta*).	Section 3.1.2 Section 5.2.2

Reviewer 5	There are some instances of inappropriate averaging using resistant life stages. Bull trout at the most sensitive (~1g) were averaged with results of test with yearling brook trout to produce a nonsense genus mean acute value of 126 µg/L. Stephan et al. advise against pooling species mean values when they differ by more than a factor of 10; these differed by a factor of 1000X.	This issue was re-examined ion depth based on the peer reviewer's comments. The SMAVs for bull trout and brook trout do differ by more than a factor of 10 (factor of 708X), most likely due the different sensitivities of the fish used to initiate the tests. The freshwater and estuarine/marine acute databases also include several genera where two or more widely different SMAVs (>10x factor) are available for estimating the GMAV. In this case the 1985 Guidelines recommend that some or all of the values probably should not be used in calculations. To resolve this issue, only the more sensitive SMAV (primarily due to a more sensitive life stage tested) was used to calculate the GMAV, thereby ensuring protection of the genus. It is important to note that the FAV can be lowered to protect the most sensitive SMAV for a commercially or recreationally important species to be conservative. This was the case for the acute freshwater value for both the 2001 AWQC and the current 2015 draft criteria update.	Table 7 Table 10 Section 5.1.3 Section 5.4.1
Reviewer 5	The draft document evaluates protection of listed species by rolling up species data to a hardness-normalized species mean acute value (SMAV) and comparing that with the criteria. Because the accuracy of hardness-normalization is uncertain, but the criteria values can be calculated with certainty for any hardness, a more informative way to evaluate the data with listed species is to compare the criteria values for the conditions of each test of interest with listed species to the effects magnitude of effects to listed species at a given criteria. If the test concentrations causing an adverse effect are close to criteria concentrations, such as if the EC50s were within a factor of 2 (or maybe 2.5 to 3 to be on the safe side), then evaluate the actual adverse effects observed at the criteria concentrations. The SMAV approach involves a lot of data manipulation and may lose sensitive life stages or strains.	The criteria document provides the available toxicity data for listed species. A separate document is in development that addresses the detailed analyses of protection of Listed salmonid species. Additionally, states and tribes have the opportunity to use the toxicity data provided in this document, as appropriate, to their address their specific situation.	Section 5.8

2.5 OTHER COMMENTS PROVIDED

Reviewer	Comments	EPA Response	Revision Location
Reviewer 4	Additional Minor Comments Page 11: Note that Cd does not form complexes with Ca as stated, but rather competes with Ca for uptake and Ca channels. Please correct.	Text was revised as suggested.	Section 2.3
Reviewer 4	Page 11: While Atli and Canli did observe a reduction in NKA activity in their study, it's a significant overstatement to say disruption of Na homeostasis is a mechanism of action for Cd. To the best of my knowledge, it hasn't been observed in any other study that has investigated this potential mechanism.	Text was revised as suggested.	Section 2.3
Reviewer 4	Page 11: If Cd inhibits catalase, glutathione reductase, SOD, etc., it seems to me this is direct inhibition of anti-oxidant processes, not indirect as stated.	Text was revised as suggested.	Section 2.3
Reviewer 4	Page 12: Regarding the relationship between Cd tissue burdens and toxicity, see also the analysis by Adams et al. (2011).	EPA recognizes the difficulty in characterizing dietary exposure and establishing critical tissue effects thresholds associated with bioaccumulated metals (the identified paper has been reviewed and text has been added to the document).	Section 5.6.1
Reviewer 4	Page 50: *Tigriopus* is a copepod, not a mysid, as indicated in the second paragraph.	Text was revised as suggested.	Section 3.2.1
Reviewer 4	Page 58: Please specific at the top of p. 58 which two freshwater ACRs were used in the calculation of the marine ACR.	Text was revised to be clearer in the selection of ACRs used to calculate the FACR.	Section 3.2.2 Section 5.5.1
Reviewer 4	Table 18: Change the test duration for the Borgmann studies to 42 d rather than 6 w to make the units consistent with the rest of the table.	Text was revised as suggested.	Table 18
Reviewer 4	Page 83: It should be mentioned that both BCFs and BAFs are inversely related to exposure concentration which explains much of the variation in BCFs/BAFs (McGeer et al. 2003, DeForest et al. 2007).	Text was revised as suggested.	Section 5.6

Reviewer 4	Table 21: Taking a final look through Table 21 I note that EPA has included several species that are not resident to N. America (*Oreochromis spp., Danio rerio, Xenopus laevis*). Unless this requirement has changed, they should be removed from the data set.	Naturally/wild reproducing North American species populations are considered for inclusion in the document. Each has been verified as such. Please see the following links for the species mentioned: http://nas.er.usgs.gov/queries/factsheet.aspx?SpeciesID=67 http://nas.er.usgs.gov/queries/FactSheet.aspx?speciesID=505 http://nas.er.usgs.gov/queries/FactSheet.aspx?speciesID=468 http://nas.er.usgs.gov/queries/FactSheet.aspx?speciesID=466	No edits
Reviewer 5	Unfortunately, the compressed time period for this review (2 weeks, which works out to several hours on evenings and weekends for volunteer reviewers), makes a comprehensive review of a document of this length and complexity infeasible.	Thank you for your comment. EPA appreciates the comments that were provided during the time available for review.	No edits

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